Delayed cyclic activity development on early amplitude-integrated eeg in the preterm infant with brain lesions

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Abstract: Background: Maturation of amplitude-integrated electroencephalogram (aEEG) activity is influenced by both gestational age (GA) and postmenstrual age. It is not fully known how this process is influenced by cerebral lesions. Objective: To compare early aEEG developmental changes between preterm newborns with different degrees of cerebral lesions on cranial ultrasound (cUS). Methods: Prospective cohort study on preterm newborns with GA <32.0 weeks, undergoing continuous aEEG recording during the first 84 h after birth. aEEG characteristics were qualitatively and quantitatively evaluated using pre-established criteria. Based on cUS findings three groups were formed: normal (n = 78), mild (n = 20), and severe cerebral lesions (n = 6). Linear mixed models for repeated measures were used to analyze aEEG maturational trajectories. Results: 104 newborns with a mean GA (range) 29.5 (24.4-31.7) weeks, and birth weight 1,220 (580-2,020) g were recruited. Newborns with severe brain lesions started with similar aEEG scores and tendentially lower aEEG amplitudes than newborns without brain lesions, and showed a slower development of the cyclic activity ($p < 0.001$), but a more rapid increase of the maximum and minimum aEEG amplitudes ($p = 0.002$ and $p = 0.04$). Conclusions: Preterm infants with severe cerebral lesions manifest a maturational delay in the aEEG cyclic activity already early after birth, but show a catch-up of aEEG amplitudes to that of newborns without cerebral lesions. Changes in the maturational aEEG pattern may be a marker of severe neurological lesions in the preterm infant.

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Title

Delayed cyclic activity development on early amplitude-integrated EEG in the preterm infant with brain lesions

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Short Title

Cyclic activity on early aEEG in the preterm

Key words

Amplitude-integrated EEG, preterm, brain lesion, cyclic activity

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Conflict of interest

All authors declare no actual or potential conflict of interest in relation to this manuscript.

Contributor´s Statement

Dr Giancarlo Natalucci had primary responsibility for the study design, data acquisition, analysis and writing the manuscript.

Drs Valentin Rousson was involved in study design, data analysis, data interpretation and writing of the manuscript.

Drs Hans Ulrich Bucher and Vera Bernet were involved in study design, data acquisition and writing of the manuscript.

Drs Cornelia Hagmann and Beatrice Latal supervised the design and execution of the study, data analyses and contributed to the writing of the manuscript.

All authors approved the final version of this manuscript to be published.

ABSTRACT

Background: Maturation of amplitude-integrated electroencephalogram (aEEG) activity is influenced by both gestational (GA) and postmenstrual age (PMA). It is not fully known how this process is influenced by cerebral lesions. **Objective:** To compare early aEEG developmental changes between preterm newborns with different degrees of cerebral lesions on cranial ultrasound (cUS). **Methods:** Prospective cohort study on preterm newborns with GA <32.0 weeks, undergoing continuous aEEG recording during the first 84 hours after birth. aEEG characteristics were qualitatively and quantitatively evaluated using pre-established criteria. Based on cUS findings three groups were formed: normal (n=78); mild (n=20); and severe cerebral lesions (n=6). Linear mixed models for repeated measures were used to analyse aEEG maturational trajectories. **Results:** 104 newborns with a mean GA (range) 29.5 (24.4-31.7) weeks, and birth weight 1220 (580-2020) grams were recruited. Newborn with severe brain lesions started with similar aEEG scores and tendentially lower aEEG amplitudes than those of newborns without brain lesions; and showed a slower development of the cyclic activity ($p<.001$), but a more rapid increase of the maximum and minimum aEEG amplitudes ($p=.002$ and $p=.04$). **Conclusions:** Preterms with severe cerebral lesions manifest a maturational delay in the aEEG cyclic activity already early after birth, but show a catch-up of aEEG amplitudes to that of newborns without cerebral lesions. Changes in the maturational aEEG pattern may be a marker of severe neurological lesions in the preterm.

Introduction

While the mortality rate of extremely preterm newborns in the last decades constantly decreased, neurodevelopmental morbidity remained almost unchanged [1]. Thus, attention has been focused on the implementation of monitoring, prevention, and treatment of brain lesion in this population. Detailed neurological examination of the preterm newborn early after birth is often impossible before the child is clinically stable, while continuous bed-side monitoring of the central nervous function can be assessed by means of the amplitude-integrated EEG (aEEG) [2]. Normative aEEG data have been established for term infants and aEEG has been shown to be a good predictive tool for unfavourable outcome in term newborns with hypoxic ischemic encephalopathy [3]. The interpretation of aEEG tracings in preterm infants, however, is different as in term newborns. Several studies focused on defining normal aEEG tracing [3-7] and its prognostic value [8] in preterm newborns. In fact, in the preterm newborn the predominant aEEG background pattern is discontinuous [3]; the aEEG trace evolution early after birth is influenced by the time of extrauterine exposure [4-6]; and the cyclical character is less defined than in term newborns [2,6,7]. Previous work has focused on the changes on aEEG in association with brain abnormalities in preterms, identifying voltage suppression and the absence of cycling activity [9-11] as markers of poor short- and long-term outcome [12]. A better knowledge on the evolution of maturational patterns of aEEG in preterms may improve early detection of brain abnormalities and outcome prediction. We therefore aimed to define the developmental trajectories of aEEG tracings over the first four days of life in preterm newborns in function of the degree of brain lesion on routine cranial ultrasound (cUS).

Patients and Methods

Subjects

This study was conducted in the Division of Neonatology of the Zurich University Hospital, Switzerland between January 2009 and July 2010. Inborn infants with a gestational age (GA) <32.0 weeks without congenital anomalies, metabolic disorders or central nervous system infections were prospectively enrolled. GA was determined by the best obstetrical estimate based on the last menstrual cycle and first trimester ultrasound scans if available. Cranial ultrasound (cUS) was obtained at day 1, 3, 7 of life, and repeated weekly until hospital discharge. Peri/Intraventricular haemorrhage (P/IVH) and periventricular leukomalacia (PVL) was defined according to Papile [13], and De Vries [14], respectively. We classified subjects according to cUS scan findings in 3 groups. Group 1 (normal cUS): without any cUS abnormalities; group 2 (mild brain lesions): with grade I-II P/IVH and/or grade I PVL; group 3 (severe brain lesions): with grade III-IV P/IVH and/or grade II-IV PVL.

Data acquisition and analysis procedure

Two-channel aEEG monitoring was recorded from biparietal hydrogel electrodes C3–P3 and C4–P4, according to the international 10–20 system, ground F_Z [15], with the Brainz BRM3 monitor (Natus Medical Incorporated San Carlos, CA, USA). The physiologic basis and aEEG engineering have been largely described elsewhere [2]. Monitoring started within the first 24h after birth and lasted until day 4. Tracings were divided in 3-hours epochs as units to be analysed. Only artefacts- and seizures free periods, with impedance <12 kOhm, were analysed. To provide comparison with single-channel aEEG monitors we analysed cross-cerebral P3–P4 aEEG tracings.

The maturity of the aEEG tracings was scored qualitatively by visual assessment of each 3h-epochs according to Burdjalov and associates [6]. Four aEEG components

were analysed: a) ‘continuity’ of the aEEG trace; b) the ‘cycling’ character of the aEEG trace; c) the average ‘amplitude of the lower border’ of the aEEG traces; and d) ‘bandwidth’ (for details see [6]). Each component was scored and individual values were summed to determine a ‘maturity total score’ for each aEEG epoch. The ‘maturity total score’ ranges from 0–13, the lower the score the more immature the brain activity. Because of its prognostic relevance in terms of brain activity maturation in the term newborn [6], the ‘cycling subscore’, ranging from 0–5, was additionally analysed. Two authors (GN, CH) blinded to the cranial ultrasound findings rated the aEEG traces off-line. Cohen’s kappa (95% CI) for inter-rater agreement was 0.79 (0.75-0.82) for the total maturity score and 0.60 (0.52-0.66) for the cycling subscore, respectively. For statistical analysis we considered one author’s aEEG scores (GN).

The BrainZ Analyze Research software (Chart analyser 1.71, The Liggins Institute, Auckland, NZ) allowed quantitative calculation of the 1-minute average values for the maximum and minimum aEEG amplitudes after export of raw EEG data [16]. For these two quantitative outcomes, the median value of each 3h-epoch has been recorded.

Statistics

We estimated the average trajectories along the first four days of life for the three groups with respect to the different aEEG measures using linear mixed models. A trajectory was hence described by a regression line for each group, and the groups were then compared with respect to their intercepts and with respect to their slopes. The parameterisation was chosen such that the intercepts were estimations of the average outcome at 0.5 days of life in the different groups. A difference of intercepts was an indication of a difference between the groups shortly after birth, whereas a difference of slopes was an indication of a difference of speed of development. Our

models included a random “infant effect” to account for the dependence among the repeated measurements made on a same infant. All models were adjusted for differences in GA; for the binary factors: gender, morphine sedation, caffeine- and indomethacin therapy, chorioamnionitis, small for gestational age status, caesarean section; and Score for Neonatal Acute Physiology Perinatal Extension II (SNAPPE II) [17]. Calculations were done using the “lme” routine from the free statistical R package (version 2.5.1).

Ethics

The institutional ethics boards of the Canton of Zurich approved the study protocol. Written informed consent was obtained from the parents.

Results

Study subjects

aEEG tracings of 104 infants with a mean GA (range) of 29.5 (24.4-31.7) weeks, and a birth weight of 1220 (580-2020) grams were evaluated. The recordings began at a mean (range) age of 15.3 (1-22) hours and were performed continuously until a mean age of 82.7 (72-120) hours after birth. Group 1 consisted of 78 infants, group 2 of 20 infants (4 with grade I and 6 grade II P/ICH, 7 with grade I PVL, and 3 with both grade II P/ICH and grade I PVL), and group 3 of 6 infants (4 with grade III P/ICH, 2 with grade III PVL). Cysts in cystic PVL emerged at 11 and 18 days after aEEG monitoring; all other cerebral lesions were detected during recording or within 24 hours after the end of the aEEG monitoring. All subjects survived to discharge except for one infant with normal cUS findings who was diagnosed with sepsis 4 weeks after birth. Except for the rate of chorioamnionitis, there were no significant differences among the groups with respect to the perinatal characteristics (Table 1).

Developmental patterns of the aEEG trace over time

Figure 1a-d displays the estimated trajectories over time for each group according to the different aEEG measures. Slopes of postnatal development were positive and strongly significant in all groups and for all aEEG measures (all $p<.001$). A positive and significant association of GA with ‘maturity total score’, ‘cycling subscore’, and ‘minimum aEEG amplitude’ was noted ($p<.001$).

Comparison between the groups

Visual aEEG assessment (Table 2, Figure 1a-1b)

With respect to the 'maturity total score' and its 'cycling subscore' the intercepts were significantly lower in group 2 than in group 1, whereas in group 3 they were similar to group 1. A comparison of the slopes yielded that group 2 had a significant faster development for both scores; whereas group 3 had a slower development than group 1, especially for the ‘cycling subscore’.

Quantitative aEEG assessment (Table 2, Figure 1c-1d)

The intercept was significantly higher in group 2 than in group 1 regarding maximum aEEG amplitude, whereas it was tendentially lower in group 3 than in group 1 for both maximum and minimum aEEG amplitude, even if not significantly so. We observed significant differences of slopes between group 3 and group 1 with respect to both maximum and minimum aEEG.

Discussion

This study describes the development of aEEG traces within the first four days of life in preterm newborns with different degrees of cerebral lesions detected by cUS. We found that preterm newborns with severe cerebral lesions had a significantly slower

development of their cyclic activity on the aEEG when compared to preterm newborns without cerebral abnormalities. However, in the quantitative analysis, preterm newborns with severe cerebral lesions showed a significant catch-up trend, indicating an initial delay followed by a rapid levelling of the aEEG measures to that of newborns without cerebral abnormalities. Both visual and mechanical aEEG measurements were positively and significantly associated to GA. This is in agreement with previous literature on normal preterm infants [4,5], and in particular with one study, in which the course of aEEG amplitudes has been analysed similarly over the first 7 days of life [12]. The association between absent cyclicity on aEEG and brain lesion has been reported in the newborn with central nervous system affection [7, 11, 18]. In term newborns, the severity of a hypoxic ischemic insult is related to a delay of onset or even an absence of sleep-wake cycling (SWC) [18]. In preterm newborns with large cerebral haemorrhages, SWC was less commonly observed than in preterms without lesions [9]. Further, the presence of SWC during the first two weeks of life was associated with good outcome in extremely preterm infants with small or no cerebral haemorrhage [19]. It is of note that the terminology regarding the cyclical aEEG activity in the preterm patient is not uniformly used. The term SWC refers to a biological pattern of alternating sleeping and waking states, which are defined with behavioural parameters together with neurophysiologic monitoring [20]. In contrast, in the preterm newborn, rudimentary cyclical variations in the aEEG background indicating sleep-wake states have been reported to occur around gestational week 25 to 27 [7,19]. This has also been observed in raw EEG tracings of stable preterm newborns [21]. Additionally, this pattern of aEEG activity at such an early developmental stage is not as distinct as it is at 35 to 36 weeks GA, where a regular and sinusoidal alternation between discontinuous and continuous background activity is clearly recognizable [3]. Regardless of the terminology, the

interpretation of early continuous aEEG monitoring in the preterm newborn is difficult regarding the recognition of cyclic activity and the evaluation of its maturational state. Interestingly, while newborns with severe brain lesions showed a delay in the maturation of the cyclic activity, a maturational catch-up was observed after an early depression in subjects with mild cerebral lesions.

In regard to the quantitative aEEG data analysis, the maximum and minimum aEEG amplitude in preterms with severe brain lesions was tendentially lower at the beginning of the observation time than in preterms with normal cUS findings and showed a significant catch up to the amplitude of newborns with normal cUS. This was not true for subjects with mild brain lesions in whom the maximum aEEG amplitude was slightly higher than in newborns without cerebral abnormalities.

As aEEG activity is suppressed in preterm infants with high illness severity scores [22], the clinical condition of the study subjects during the observational period could have influenced the aEEG maturation. We therefore adjusted for the Score for Neonatal Acute Physiology Perinatal Extension II [17], a measure of illness severity and mortality in newborns in the comparison between brain injury groups.

We hypothesize that different maturational patterns might reflect the different degree of altered functional brain maturation, or dysmaturity, depending on the underlying neuronal damage [23]. Thus, the deficit in the maturation of the cyclic activity in the aEEG of preterms should be considered a marker of altered brain plasticity in the presence of severe brain lesion. The development of the SWC involves multiple interconnected neuronal networks [24], this may explain why aEEG cycling characteristics best reflected the severity of brain lesion in our work. A similar phenomenon has been observed in response to environmental stress during neonatal care [25]. Further investigation with combined electrophysiological (i.e. multichannel EEG), neuroimaging (i.e. diffusion tensor imaging), and clinical (i.e.

behavioural) assessments is needed in order to clarify the pathophysiological substrate and a possible association with the long-term outcome of the patient.

The strengths of this study consists in the statistical analysis which is based on a maturation-curve modelling, allowing for a comparison of the development trajectories of subjects grouped in function of their cranial ultrasound finding, and a correction for different perinatal variables.

A limitation of this work is the unequal distribution of subjects in the three groups. This reflects however, the differences in the incidences of severe neonatal brain lesions in the Swiss preterm population [26]. Despite the small sample size and thanks to the repeated measurements along time, we had enough statistical power to detect a significant difference in the slopes describing the aEEG trajectories. However, we had not enough statistical power to detect difference of intercepts between these two groups. Another limitation is that not all newborns delivered in our centre were monitored as we had only two aEEG devices. This could have caused recruitment bias. However, the 104 recruited newborns and the 148 dropouts fulfilling the inclusion criteria were similar with respect to GA, BW, gender, arterial cord pH, 5' Apgar score, and distribution of brain lesions on cUS (data not shown). Finally, our inter-rater agreement for the visual aEEG assessment was of moderate degree, which may reduce the confidence in the results.

In conclusion, our results show that preterm newborns with severe cerebral lesions manifest a maturational delay in the aEEG cyclic activity already early after birth, and they show a catch-up of aEEG maximum and minimum amplitudes to that of newborns without any lesion. These findings are relevant for the interpretation of the continuous neuromonitoring in preterm <32 weeks GA, highlighting the role of the maturational changes of the cyclic activity as a possible marker for early identification

of patients at particular risk for brain lesion. The significance of these changes for neurodevelopment outcome needs to be determined.

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366 **Table 1: Comparison of perinatal characteristics of newborns with normal cUS**

367 **finding versus newborns with mild and severe brain lesion**

368

Groups according to cUS finding	1 Normal finding n = 78	2 Mild brain lesion n = 20	3 Severe brain lesion n = 6	p-value *
Gestational age (weeks) m (range)	29.6 (24.4 – 31.9)	29.7 (26.1 – 31.7)	28.1 (25.3 – 30.0)	n.s.
Below 28 gestational weeks, n (%)	14 (18)	4 (20)	3 (50)	n.s.
Birth weight (grams) m (range)	1250 (580 – 2020)	1240 (620 – 1780)	1140 (740 – 1550)	n.s.
Below 1000 grams, n (%)	23 (29)	4 (20)	2 (33)	n.s.
Small for gestational age, n (%)	13 (17)	1 (5)	1 (17)	n.s.
Gender/Male, n (%)	42 (54)	11 (55)	3 (50)	n.s.
Preeclampsia, n (%)	19 (24)	2 (10)	0	n.s.
Chorioamnionitis/Funisitis, n (%)	14 (18)	8 (40)	2 (33)	n.s.
Caesarean section, n (%)	69 (88)	13 (65)	4 (66)	.03
Arterial Cord pH, m (SD)	7.30 (0.10)	7.30 (0.08)	7.28 (0.03)	n.s.
5’ Apgar, m (range)	6.8 (1 – 8)	6.5 (2 – 9)	5.7 (3 – 8)	n.s.
Days on artificial ventilation, M (IQR)	0 (0 – 2)	0 (0 – 0.5)	1 (0 – 3)	n.s.
Respiratory distress, n (%)	70 (90)	20 (100)	6 (100)	n.s.
Surfactant, n (%)	14 (18)	3 (15)	3 (50)	n.s.
SNAPPE II, M (IQR)	18 (5 – 28)	9 (0 – 27)	20 (9 – 36)	n.s.
Sedation while aEEG, n (%)	12 (15)	2 (10)	1 (17)	n.s.
Caffeine, n (%)	18 (23)	4 (20)	3 (50)	n.s.
Indomethacin, n (%)	21 (27)	2 (10)	2 (33)	n.s.

369

370 cUS: cranial ultrasound; mild brain lesion: intraventricular hemorrhage grade I-II
371 and/or periventricular leukomalacia grade I; severe brain lesion: intraventricular
372 hemorrhage grade III-periventricular hemorrhage and/or periventricular leukomalacia
373 grade II-III. SNAPPE II = Score for Neonatal Acute Physiology Perinatal Extension II
374 [17]; m = mean; SD = standard deviation, M = median, IQR = interquartile range.
375 * Analysis of variance (ANOVA) and Kruskal-Wallis-test for continuous data, Chi-
376 square test for categorical data.

Table 2: Comparison of the groups with respect to each aEEG assessment method using a linear mixed model.

		Comparison of aEEG measurements at time 0.5 days of life (intercepts)		Comparison of aEEG development speed over the first 4 days of life (slopes)	
Figure Number	aEEG assessment method	Group 2 versus 1	Group 3 versus 1	Group 2 versus 1	Group 3 versus 1
1a	Maturity total score	−1.05 (−2.01 ; −0.10) *p = .03*	−0.65 (−2.29 ; 1.00) *p = .44*	0.34 (0.17 ; 0.51) *p < .001*	−0.25 (−0.51 ; 0.02) *p = .07*
1b	Cycling subscore	−0.40 (−0.78 ; −0.3) *p = .04*	−0.01 (−0.65 ; 0.62) *p = .96*	0.10 (0.03 ; 0.16) *p = .005*	−0.19 (−0.30 ; −0.09) *p < .001*
1c	Maximum aEEG amplitude	2.66 (0.39 ; 4.93) *p = .02*	−2.65 (−6.53 ; 1.24) *p = .18*	−0.15 (−0.71 ; 0.42) *p = .61*	1.36 (0.50; 2.23) *p = .002*
1d	Minimum aEEG amplitude	0.21 (−0.30 ; 0.73) *p = .38*	−0.63 (−1.51 ; 0.24) *p = .11*	−0.09 (−0.23 ; 0.05) *p = .20*	0.23 (0.01 ; 0.45) *p = .04*

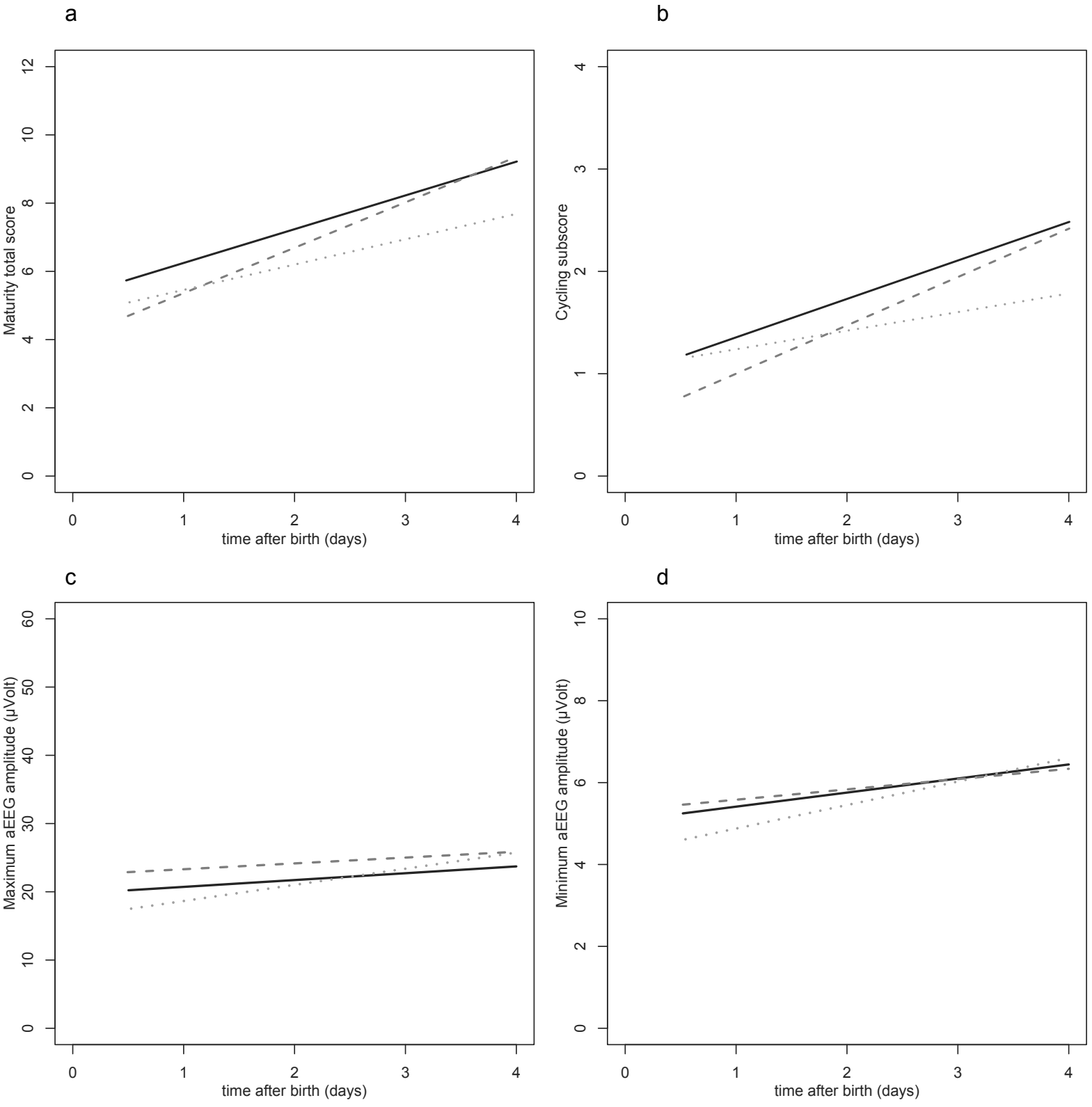
Differences of intercepts and slopes (describing aEEG trajectories along the first four days of life) between group 2 and group 1, and between group 3 and group 1, together with 95%-confidence intervals and the corresponding p-values obtained using a linear mixed model. Group 1: infants with normal cranial ultrasound finding; group 2: infants with mild cerebral lesion; group 3: infants with severe cerebral lesion. All results have been adjusted for gestational age, gender, morphine sedation, caffeine- and indomethacin-therapy during aEEG, as well as small for gestational age status, chorioamnionitis, caesarean section, and the Score for Neonatal Acute Physiology Perinatal Extension II [17].

Figure legend

Figure 1a-1d

Average aEEG trajectories (representing the postnatal development) during the first four days of life for the three groups and the four aEEG outcomes (a, maturity total score; b, cycling subscore; c, maximum aEEG amplitude; d, minimum aEEG amplitude) estimated using linear mixed models. Group 1: infants with normal cranial ultrasound finding (continuous black line); group 2: infants with mild cerebral lesion (dashed grey line); group 3: infants with severe cerebral lesion (dotted grey line). Lines are starting at 0.5 days of life, respectively at begin of the observational time which was slightly different for the three groups and the different outcomes. All results were adjusted for gestational age, gender, morphine sedation, caffeine- and indomethacin-therapy during aEEG, as well as small for gestational age status, chorioamnionitis, caesarean section, and the Score for Neonatal Acute Physiology Perinatal Extension II [17].

Figure 1a-d


a
Maturity total score
0
2
4
6
8
10
12
0
1
2
3
4
time after birth (days)
b
Cycling subscore
0
1
2
3
4
0
1
2
3
4
time after birth (days)
c
Maximum aEEG amplitude (µVolt)
0
10
20
30
40
50
60
0
1
2
3
4
time after birth (days)
d
Minimum aEEG amplitude (µVolt)
0
2
4
6
8
10
0
1
2
3
4
time after birth (days)